IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: MUSKULUS, Frank et al.	
	Art Unit: 1616
Serial No.: 10/522,784	Examiner: Choi, Frank I.
Filed: Feb. 24, 2005	Atty. Docket: 966927.10017
For: *Pharmaceutical Preparation Containing a Benzimidazole Compound Mixed with Microcrystalline Cellulose and a Method for Its Preparation*	

DECLARATION UNDER 37 C.F.R. § 1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, Frank Muskulus, declare that I am one of the named applicants of the above-referenced patent application and I am one of the co-inventors of the subject matter described and claimed therein. I am also familiar with the teachings of Shimizu et al. (U.S. Patent 5,824,339; hereinafter, "the '339 patent").

As described herein, my co-inventors and I made the surprising and entirely unexpected observation that microcrystalline cellulose acts as a stabilizer of benzimidazole compounds of formula I, such as omeprazole, lansoprazole, rabeprazole and pantoprazole, as described in the above-referenced application. We also observed that stability of certain benzimidazole compounds is achieved by combining the benzimidazole compound in mixture with microcrystalline cellulose. This surprising and completely unexpected discovery would not have been obvious in view of the '339 patent or in view of any other teachings of the prior art.

There has been a long-felt need in the prior art to achieve stability of such benzimidazole compounds of formula I. The difficulty of providing sufficiently stable

pharmaceutical preparations that contain these benzimidazole compounds was well known. Since it was conventionally known that benzimidazole compounds of formula I, in particular omeprazole, are labile in an acidic aqueous solution, benzimidazole compounds were routinely combined in formulations with an alkaline buffer. The many problems inherent to such conventional formulations are discussed, for example, in European patent publication EP-A 0 247 983.

Thus, our finding that microcrystalline cellulose is capable of stabilizing benzimidazole compounds of formula I, in particular omeprazole, pantoprazole, rabeprazole and lansoprazole, was completely unexpected. We unexpectedly observed that when microcrystalline cellulose is used for stabilizing such benzimidazole compounds in a layer of a pellet containing the active ingredient, it is especially advantageous if the microcrystalline cellulose particles are as small as possible in size, and it is presumed that stabilization occurs through interaction with the extensive surfaces of the microcrystalline cellulose.

Our benzimidazole-containing formulations include pellets with an inert core to which a layer containing an active ingredient is applied. The layer with the active substance applied to the core contains the active ingredient, the benzimidazole compound and the microcrystalline cellulose in addition to other optional, pharmaceutically compatible excipients. Applied to the layer with active ingredient are preferably one or more inert layers (separating layers), and the pellet has an outer layer comprising an enteric layer. We discovered that the amount of microcrystalline cellulose in the layer containing the active ingredient can be varied across a broad range. For instance, we observed that the amount of microcrystalline cellulose in the layer with the active ingredient can vary, for instance, 10 to 150%, 25 to 150%, or 50 to 150% by weight based on the amount of active ingredient.

We also observed that the active ingredient may be dispersed together with the excipients, in particular the microcrystalline cellulose and the binder, in a suitable solvent, preferably water, and the aqueous dispersion is then sprayed on the neutral pellets. We discovered that the unexpected stabilizing effect of the microcrystalline cellulose is particularly notable if this type of manufacturing process is used.

We prepared several formulations containing microcrystalline cellulose as described below in Examples 1, 2 and 3. We then analyzed decomposition of the benzimidazole compounds in our formulations (Examples 1, 2 and 3), as compared to conventionally prepared formulations in which the benzimidazole compound was not combined with microcrystalline cellulose (Comparative Examples 1 and 2).

Comparative Example 1 (a conventional preparation in which an alkaline-reacting compound was used)

6.7 kg of Type 603 hydroxyproplymethylcellulose was dissolved in 50 liters of de-mineralized water. In a second preparation 1.0 kg of Na_2HPO_4 (alkaline-reacting compound) was initially dissolved in 5 liters of de-mineralized water. In this second solution 13.3 kg of omeprazole was dispersed with an Ultra-Turrax. Finally, 1.0 kg of polysorbate 80 was mixed with the dispersion containing the active ingredient. Both solutions/dispersions were slowly combined and carefully stirred. The entire mixture was then sprayed on 36.5 kg of neutral pellets in a conventional fluidized bed apparatus suitable for such purpose (e.g. Glatt-Wurster-type apparatus). Rate of spray and inlet air temperature are regulated to obtain a product temperature of about 35 to 40 °C. A separating layer and an enteric coating was then applied to the pellets containing the active ingredient. Polyethlyeneglycol (PEG) was used in preparing the enteric coating.

Comparative Example 2 (another conventional preparation in which an alkaline-reacting compound was used)

Pellets containing omeprazole were produced in a similar manner to those in Comparative Example 1, in which however triethylcitrate was used instead of polyethlyeneglycol as a plasticizer in the application of the enteric coating.

Example 1 (one of our preparations in which the benzimidazole compound was combined with microcrystalline cellulose)

2.8 kg of omeprazole and 1.4 kg of microcrystalline cellulose of the type AVICEL-PH®-105 from FMC (mean particle size 20 µm, granular size distribution such that less than 0.1% of particles are 250 µm or larger in size and less than 1% of particles are 75 µm or larger in size) were dispersed by means of an Ultra-Turrax in 15.8 kg of de-mineralized water. 2.8 kg of hydroxypropylmethylcellulose was dissolved in a second preparation also in 15.8 kg of de-mineralized water. Both preparations were combined and lightly stirred, then applied to 2.8 kg of neutral pellets. A separating layer was applied using 1.6 kg microcrystalline cellulose of the type AVICEL-PH®-105 and 3.1 kg of HPMC in 35 kg of de-mineralized water. Next, an enteric coating was applied, using a dispersion of 17.5 kg of Eudragit L30D55 partly neutralized by sodium hydroxide, 1.3 kg PEG 6000, 200 g of glycerol monostearate and 14.9 kg of de-mineralized water. The coating was applied by spraying.

Example 2 (another one of our preparations in which the benzimidazole compound was combined with microcrystalline cellulose)

Pellets containing an active ingredient were manufactured in the manner described in Example 1 with lansoprazole as the active ingredient.

Example 3 (another one of our preparations in which the benzimidazole compound was combined with microcrystalline cellulose)

In the same manner as described in Example 1, pellets containing an active ingredient were manufactured using omeprazol. The pellets were compressed into a "multiple unit dosage form" in accordance with conventional techniques.

Example 4

The pellets of the Comparative Examples 1 and 2, and of Examples 1, 2 and 3 were subjected to a conventional storage test under open conditions (40 °C/75% relative humidity), and decomposition of the active ingredient after four weeks in storage was determined in accordance with known methods. The following table summarizes the results of the storage test.

Preparation	Comparative Example 1	Comparative Example 2	Example 1	Example 2	Example 3
Decomposition of the benzimidazole compound at 40 °C/75% relative humidity, open storage, after 4 weeks	48.7%	45.4%	16.5%	3.3%	13.0%

The results as shown in the table were completely surprising and unexpected. The results unexpectedly revealed that there is significantly less decomposition of the benzimidazole compound in our pharmaceutical preparations (according to Examples 1, 2 and 3) as compared with the conventional preparations in which the benzimidazole compound was not combined with microcrystalline cellulose. To eliminate all possible doubt as to the stabilizing effect of the microcrystalline cellulose, a somewhat thicker layer was chosen for the enteric coatings in the Comparative Examples; thus the pellets of the Comparative Examples would more likely be expected to provide improved stabilization of the active ingredient. Despite this thicker layer for the enteric coatings in the Comparative Examples, there was still significantly less decomposition of the benzimidazole compound in our pharmaceutical preparations (Examples 1, 2 and 3).

Example 5

The stability of the pellets according to Example 1 was compared with the stability of the commercial product ANTRA MUPS®. ANTRA MUPS® is a "multiple unit dosage form" with omeprazole as active ingredient, that is, pellets containing omeprazole compressed into tablet form. Under the same conditions as described above (open storage for 4 weeks at 40 °C and 75% relative humidity), decomposition of the active

ingredient in the ANTRA MUPS® product after 4 weeks reached 25% as opposed to just 13% in our pharmaceutical preparation of Example 3. These results again demonstrate the completely surprising and unexpected stabilizing effect achievable using our preparations through the combination of microcrystalline cellulose with a benzimidazole compound of formula I.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patents issuing thereon.

Respectfully submitted,

Frank Muskulus